CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MEPIQUAT CHLORIDE

Chemical Code # 002075, Tolerance # 00384
SB 950 # 303

August 4, 1994

I. DATA GAP STATUS

Combined toxicity, Rat	##	Data gap, study inadequate, no adverse effect
Combined toxicity, Mouse	##	Data gap, study inadequate, no adverse effect
Chronic toxicity, Rat:	##	Data gap, study inadequate, no adverse effect
Chronic toxicity, Dog:	##	Data gap, study inadequate, no adverse effect
Oncogenicity, Rat:		See combined toxicity, rat.
Oncogenicity, Mouse:	##	Data gap, study inadequate, no adverse effect
Reproduction, Rat:	##	Data gap, study inadequate, no adverse effect
Teratology, Rat:	##	Data gap, study inadequate, no adverse effect

Teratology, Rabbit: ## Data gap, study inadequate, no adverse effect
Gene Mutation: ## Data gap, study inadequate, no adverse effect

Chromosome effects: ## Data gap, study inadequate, no adverse effect

DNA damage: Data gap, no study submitted

Neurotoxicity: Not required at this time

Toxicology one-liners are attached.

All record numbers through 130820 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study/worksheet on file but not yet given a final review. A preliminary one-liner (##) and data gap status is temporarily entered into this Toxicology Summary and are subject to change pending the final review.
File name: T940800
Original: Kishiyama, 8/00/94

NOTE: One-liners with a check mark (!) needs approval (prepared by other than the toxicologist indicated).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

! 002 31127, "Chronic Oral Toxicity of 1,1-Dimethylpiperidinium Chloride, Reg.No. 85559, Tech. - called for short "DMP" - in The Sprague Dawley Rat, (F. Leuschner, A. Leuschner, K. Klie, W. Dontenwill and P. von Rogulja, Laboratorium Fur Pharmakologie und Toxikologie, Report C 20 A, 9/18/79). 1,1-Dimethylpiperidinium Chloride was admixed with the feed at concentrations of 0, 100, 300, 1000, 3000 and 9000 ppm and fed to 100, 50, 50 50, 50 and 30, respectivly, Sprague-Dawley rats/sex/group for 104 weeks. Five additional rats/sex each control and two highest dose groups were included for sacrifice at 52 weeks. UNACCEPTABLE. (Insufficient data for assessment; too few high dose animals). (C. Aldous, 8/23/85).

NOTE: Study (13 40829 & 14 4083) below is the same study as 02 31127, but contains additional data.

13, 14 and 2, 40829, 40830 & 31127, "Chronic Oral Toxicity of 1,1-Dimethylpiperidinium Chloride, Reg 85 559, Technical - Called for Short "DMP" - in the Sprague-Dawley Rat", F. Leuschner, A. Leuschner, R/ Klie/R. Stehr, W. Dontenwill and P. von Rogulja, Laboratorium Fur Pharmakologie und Toxikologie, Report C 20 A, August 1979). Reg. 85 559, admixed with the feed at concentrations of 0, 100, 300, 1000, 3000 and 9000 ppm and fed to 100, 50, 50 50, 50 and 30, respective, Sprague-Dawley rats/sex/group for 104 weeks. Five additional rats/sex each control and two highest dose groups were included for sacrifice at 52 weeks. Body weight was retarded (11-14%) for the 9000 ppm group and temporarily retarded (up to 14%) for the 3000 ppm group; NOEL = 1000 ppm. UNACCEPTABLE. Not upgradeable (too few test animals for the 9000 ppm dose level. (Kishiyama, 8/8/94)

COMBINED, MOUSE

! 002 31128, "Chronic Oral Toxicity of 1,1-Dimethylpiperidinium Chloride, Reg 85 559, Technical - Called for Short "DMP" - in the NMRI Mouse", (F. Leuschner, A. Leuschner, R/ Klie/R. Stehr, W. Dontenwill and P. von Rogulja, Laboratorium Fur Pharmakologie und Toxikologie, Report C 21 A, July 20, 1979). Reg. 85 559, admixed with the feed at concentrations of 0, 100, 300, 1000, and 3000 ppm and fed to 100, 50, 50, 50, and 50, respectively, NMRI mice/sex/group for 104 weeks. No apparent toxicity nor oncogenicity up to the HDT of 3000 ppm. UNACCEPTABLE. (No individual data to permit final judgement). UNACCEPTABLE. (C. Aldous, 8/23/85).
NOTE: Study below (040828) is the same as the above (31127) but with added data.

012 040828, "Chronic Oral Toxicity of 1,1-Dimethylpiperidinium Chloride, Reg 85 559, Technical - Called for Short "DMP" - in the NMRI Mouse", (F. Leuschner, A. Leuschner, R/ Klie/R. Stehr, W. Dontenwill and P. von Rogulja, Laboratorium Fur Pharmakologie und Toxikologie, Report C 21 A, July 20, 1979). Reg. 85 559, admixed with the feed at concentrations of 0, 100, 300, 1000, and 3000 ppm and fed to 100, 50, 50, 50, and 50, respectively, NMRI mice/sex/group for 104 weeks. There were no evidence of treatment related oncogenicity; ONCO NOEL = >3000 ppm. Body weight retardation (5% to 6%) during months 8-12 was not apparent at the end of two years for 1000 and 3000 ppm males. UNACCEPTABLE. (justification for high dose selection not given, no MTD; no individual data (food consumption and body weight) with summary at 1 week intervals; dosing material stability not confirmed). (Kishiyama, 7/9/94).

CHRONIC TOXICITY, RAT

038 130816, "Chronic Toxicity Study with Mepiquat Chloride in Wistar Rats - Administration Via the Diet over 24 Months", (W. Mellert, BASF Aktiengesellschaft, Department of Toxicology, FGR. Project No. 71S0112/89091, 5/3/94). Mepiquat chloride, purity 58%, admixed with the feed at concentrations of 0, 290, 2316 and 5790 ppm was fed to 20 Wistar rats/sex/group for 24 months. Body weight and food consumption were reduced for the high

dose groups and urinary crystals increased for high dose males; NOEL = 2316 ppm (126 mg/kg). UNACCEPTABLE. (Test article not of technical grade). (Kishiyama, 7/20/94).

Subchronic Study:

028 115514, "Study on the Oral Toxicity of Mepiquat Chloride in Wistar Rats Administration in the Diet over 3 Months", (K. Schilling, BASF Aktiengesellschaft, BASF Doc. No. 92-10433, 5/15/92). Mepiquat chloride, 57.9% ai, admixed with the feed at concentrations of 0, 145, 579, 2316, and 4632 ppm were fed to 10 Wistar rats/sex/group for 3 months. Reduced food consumption and retarded body weight were transient for the high dose group and in the absence of other effects, considered due to reduced food palatability. No worksheets. (Kishiyama, 8/11/94).

029 115515, "Supplementary Study on the Oral Toxicity of Mepiquat Chloride in Wistar Rats Administration in the Diet over 3 Months", (K. Schilling, BASF Aktiengesellschaft, BASF Doc. No. 92-10434, 5/18/92). Mepiquat chloride, 57.9% ai, admixed with the feed at concentrations of 0 and 12000 ppm were fed to 10 Wistar rats/sex/group for 3 months. Food consumption was reduced 8%-19% and body weights 17-32% for the 12000 ppm group. Overt signs (clinical) of toxicity were also observed for the 12000 ppm group. No worksheets. (Kishiyama, 8/11/94).

CHRONIC TOXICITY, DOG

022 91025, "Report on the Study of the Toxicity of Reg. No. 85 559 in Beagle Dogs Administration Via the Diet over 12 Months", (Hellwig, BASF Aktiengesellschaft, Project No. 33D0453/8565, 9/25/89). Reg. No. 85 559, purity 99.5% was admixed with the feed at concentrations of 0, 200, 600 and 1800 ppm and fed to 6 Beagle dogs/sex/group for 12 months. NOEL = 600 ppm for males; iron pigment storage was slightly increased for high dose males. NOEL for females not established. UNACCEPTABLE. No definitive toxic effects. No MTD. (Kishiyama, 7/14/94).

042 130820, "Supplementary Study of the Toxicity of Mepiquat Chloride in Beagle Dogs - Administration Via the Diet over 12 Months", (W. Mellert, BASF Aktiengesellschaft, Proj. No. 33D0001/92001, 5/5/94). Mepiquat chloride, purity 56.05%, admixed with the feed at concentrations of 0 and 8000 ppm was fed to 6 Beagle dogs/sex/group. Treatment was halted after the death (first day of treatment) of three high dose dogs (1 male and 2 females). The study was resumed for 12 months after a 5 day no treatment period, replacement of dead dogs and lowering the dose to 6000 ppm. No definitive toxic effects. Males and females were observed salivating after feeding on mepiquat chloride (6000 ppm) treated feed. Microscopic examination revealed epithelial vacuolization of renal distil tubules in treated males and females and increased hemosiderin storage in the spleen of treated males. The reported NOAEL = < 6000 ppm. The death of a 6000 ppm female implicates a treatment effect. Supplemental study. (Kishiyama, 7/15/94).

041 130819, Range-finding study for a supplementary 12-month feeding study (vol 42, record #130820.831). " The Toxicity of Mepiquat Chloride in Beagle Dogs - Administration Via the Diet over 4 Weeks", (W. Mellert, BASF Aktiengesellschaft, Department of Toxicology, FGR, Project No. 30D112/89109, 5/5/94). Mepiquat chloride, purity 56.05%, admixed with the feed at concentrations of 0, 6000 and 12000 ppm was fed to 2 Beagle dogs/sex/group for 4 weeks. Salivation after feeding was observed for all males, the surviving high dose female, and one low dose female. The premature death of one 12000 ppm female was attributed to treatment. Study has major deficiencies. NOEL not established. (Kishiyama, 7/15/94).

ONCOGENICITY, RAT

No study submitted; see combined, rat

ONCOGENICITY, MOUSE

039 130817, "Carcinogenicity Study with Mepiquat Chloride in B6C3F1 Mice - Administration in the Diet for 24 Months", (W. Mellert, BASF Aktiengesellschaft, Department of Toxicology, FGR. Proj. No. 80S0112/89107, 5/4/94). Mepiquat chloride, purity 58%, admixed with the feed at concentrations of 0, 500, 2000 and 7500 ppm was fed to 50 BC6C3F1 mice/sex/main groups for 24 months and to 10 mice/sex/satellite groups for 12 months. Body weight was slightly retarded (5-8%) for the high dose male group; NOEL for males = 2000 ppm/day; NOEL for females not established. UNACCEPTABLE. (Test article not of technical grade; no MTD for females). (Kishiyama, 7/28/94).

REPRODUCTION, RAT

040 130818, "Reproduction Toxicity Study with Mepiquat Chloride in Rats - Continuous Dietary Administration over Two Generations", (J. Hellwig, BASF Aktiengesellschaft, Department of Toxicology, FGR", Proj. No. 70R0112/89090, 10/2/93). Mepiquat chloride, purity 58%, admixed with the feed at concentrations of 0, 500, 1500 or 5000 ppm was fed to 25 Wistar rats/sex/group/generation. Treatment commenced when rats were "immature" (eventual F0 parents), continued through the reproduction of 2 litters (F1a and F1b), and ended at the F2 weanling stage. Body weight, morphological development (auditory canal opening, eye opening and gripping reflex) and the number of new-born (F2) were reduced for high-dose pups. Fewer numbers of high and mid-dose pups had eye opening on time. Reproductive NOEL = 1500 ppm; Developmental NOEL = 500 ppm. Body weight and food consumption was reduced; and the incidence of hypersensitivity, tremors and possibly mortality (F1) were increased for parental high dose rats; Maternal NOEL = 1500 ppm. UNACCEPTABLE. (test article not a technical). (Kishiyama, 7/27/94).

! 002 31129, "Chronic Toxicity of 1,1-Dimethylpiperidinium Chloride, Reg.No. 85559, Tech. - called "DMP" - in Three Succeeding Generations of Sprague Dawley Rats at Oral Administration", (F. Leuschner, A. Leuschner, G. Stehr and W. Dontenwill, Laboratorium Fur Pharmakologie und Toxikologie, 9/18/79). 1,1-Dimethylpiperidinium Chloride was admixed with the feed at concentrations of 0, 319.1, 1063.8 and 3191.5 ppm and fed to 40 Sprague-Dawley rats/sex/group for 3 generations (2 litters/generation. Twenty dams delivered and 20 were C-sectioned/generation. No maternal toxicity and no reproductive effects observed for any dose level. UNACCEPTABLE. Not upgradeable (dose selection not justified, insufficient data). (C. Aldous, 8/26/85).

016 40832. Same study as 31129, except for additional data. However, UNACCEPTABLE: dose level not justified - MTD not approached. (no worksheet). (Kishiyama, 7/9/94).

TERATOLOGY, RAT

027 114652, "Study of the Prenatal Toxicity of Mepiquat Chloride in Rats after Oral Administration (Gavage)", (J. Hellwig, BASF Aktiengesellschaft, Project No. 30R0112/89102, 4/7/92). Mepiquat Chloride, 57.9% ai, administered by gavage at concentrations of 0, 50, 150 and 300 mg/kg to 20 pregnant Wistar female rats/group during gestation days 6 through 15. Food consumption and body weight gain were significantly less; and the incidences of tremor, hypersensitivity, ataxia, withdrawn flanks and piloerection were increased at the high dose; NOEL = 150 mg/kg/day. No evidence of teratogenicity; Developmental NOEL = 300 mg/kg/day. UNACCEPTABLE. (Test article is not of technical grade). (Kishiyama, 8/10/94).

! 004 31119. "Study of the Prenatal, Perinatal and Postnatal Toxicity of 1,1-Dimethylpiperidinium Chloride on Rats" (BASF Gewerbehygiene und Toxikologie, 8/5/77). 1,1-Dimethylpiperidinium Chloride was admixed with the feed at concentrations of 0, 100, 300, 1000 and 3000 ppm and fed to 25 and 10 Sprague-Dawley rats for 0 to 20 days post coitum and 0 to 21 days post partum, respectively. No clear-cut effects relating to teratogenicity, reproductive

effects, nor maternal toxicity at any dose level. UNACCEPTABLE. Not upgradeable (Dose selection not justified). C. Aldous, 8/23/85).

TERATOLOGY, RABBIT

17 45515, "Study to Determine the Prenatal Toxicity of 1,1-Dimethylpiperidinium Chloride", (J. Merkle, Study Director, BASF Aktiengesellschaft, 9/22/81). Mepiquat Chloride, purity 99%, administered at concentrations of 0, 1.5% (75 mg/kg) and 2% (100 mg/kg) to Himalayan rabbits/group for 12 days. UNACCEPTABLE. Not upgradeable (Too few dose levels; low dose not low enough). (Kishiyama, 8/2/94)

15 040831. Same study as 45515.

17 45516, "Study of the Prenatal Toxicity of 1,1-Dimethylpiperidinium Chloride (Reg. No. 85559)", (J. Merkle, Study Director, BASF Aktiengesellschaft, 2/14/79). Mepiquat Chloride, purity 99%, administered via gavage at concentrations of 0, 50, 100 and 150 mg/kg to 21-22 artificially inseminated Russian female rabbits/group during days 6 through 18 of gestation. There were no evidence of teratogenicity; Developmental NOEL = >150 mg/kg/day. Maternal body weight, food consumption and the number of dams (abortion/maternal death) with viable fetuses were reduced during treatment for mid and high dose groups; Maternal NOEL = 50 mg/kg/day. UNACCEPTABLE. Not upgradeable (no justification of dose selection; too few number of dams with viable fetuses at scheduled termination). (Kishiyama, 8/4/94).

GENE MUTATION

023 91026, "Report on Testing of Reg. No. 85 559 (Mepiquat Chloride) in the Ames Test", (H. Zeller, BASF Aktiengesellschaft, Department of Toxicology, FGR, BASF 79/0035, 6/5/79. Reg. No. 85 559, purity. Mutagenic effects were not indicated for Reg. No. 85 559 doses tested in this study. UNACCEPTABLE. Not upgradeable (Dose selection not justified). (Kishiyama, 9/28/94).

023 91028, "Report on the Mutagenicity Test on Mepiquat Chloride in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay", (M.A. Cifone, Hazleton Laboratories America, Inc., HLA Study No.: 9680-0-447, 9/15/87). Mepiquat Chloride (Reg. No. 85 559), purity 99.86%, at concentrations of 0.026 to 1020 µg/ml in trial 1 and 25.6 µg/ml to 5000 µg/ml in trial 2 and after an eighteen hour exposure period on rat hepatocytes evaluated for mutagenicity. Mepiquat chloride was toxic to rat hepatocytes at doses 4000 and 5000 µg/ml. No evidence of mutagenicity for Mepiquat Chloride dose levels 3000 µg/ml and lower. UNACCEPTABLE. Upgradeable (no dosing material analysis, no individual data). (Kishiyama, 8/2/94)

CHROMOSOME EFFECTS

023 91027, "Clastogenic Evaluation of Mepiquat Chloride in an Iν ϛιτρο Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", (R.D.F.M. Taalman, Hazleton Biotechnologies, HBC Study No. E-9728-0-437, 12/4/87). Mepiquat chloride, purity 99%, at concentrations of 0 (McCoy's medium), 2, 3, 4, and 5 mg/ml with and without metabolic activation (S-9 Mix) were evaluated for mutagenicity using Chinese hamster (CHO) ovary cells; exposure time was 2 and 7.8 hours, with and without S-9 Mix, respectively. There were no evidence of increased aberrations with Mepiquat chloride treatments. UNACCEPTABLE (no analysis of dosing solution). (Kishiyama, 8/1/94).

! 004 31120. "Examination of 1,1-Dimethylpiperidinium Chloride Reg. No 85559, Tech. - Called "DMP" - for Mutagenic Properties (Dominant Lethal Genes) in Mice at Oral Administration", (F. Leuschner, Laboratorium fur Pharmakologie and Toxikologie, 5/9/79). DMP, purity not stated, admixed with the feed at concentrations of 0, 100, 300, 1000 and 3000 ppm/day and fed to 20 NMRI males/group for 5 days prior to breeding. Twenty additional untreated males/group served as controls. Males (treated and untreated) were mated with untreated females. No dominant lethal effects and/or other treatment related effects up to the highest dose tested (3000 ppm). UNACCEPTABLE. Not upgradeable (no justification of high dose selection). (C. Aldous, 8/23/85).

DNA DAMAGE

No study submitted.

NEUROTOXICITY